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(54) Title: MEDICAL PREPARATIONS CONTAINING N-METHYLATED CYCLIC UNDECAPEPTIDES

(57) Abstract

Medical preparations (drugs) cntaining N-methylated cyclic undecapeptides, especially for internal use, characterized by the presence of 0.1 to 20 weight parts of compounds from the group of cyclosporins (A), 0.3 to 60 weight parts of emulsifier (B) containing anhydromanitol oleylether and/or lactoglyceride and/or citrogylceride, 0.1 to 10 weight parts of emulsion stabilizer (C) containing aluminium-magnesium hydroxy-stearate as a lipogel and 0.2 to 40 weight parts of a solvent (D) composed of 1,4 : 3,6-dianhydro-2,5-di-O-methyl-D-glucitole and/or 1,3-dimethyl-2-imidazolidone and/or ethanol, with the ratio A:B being equal to 1:0.5 - 1:30.

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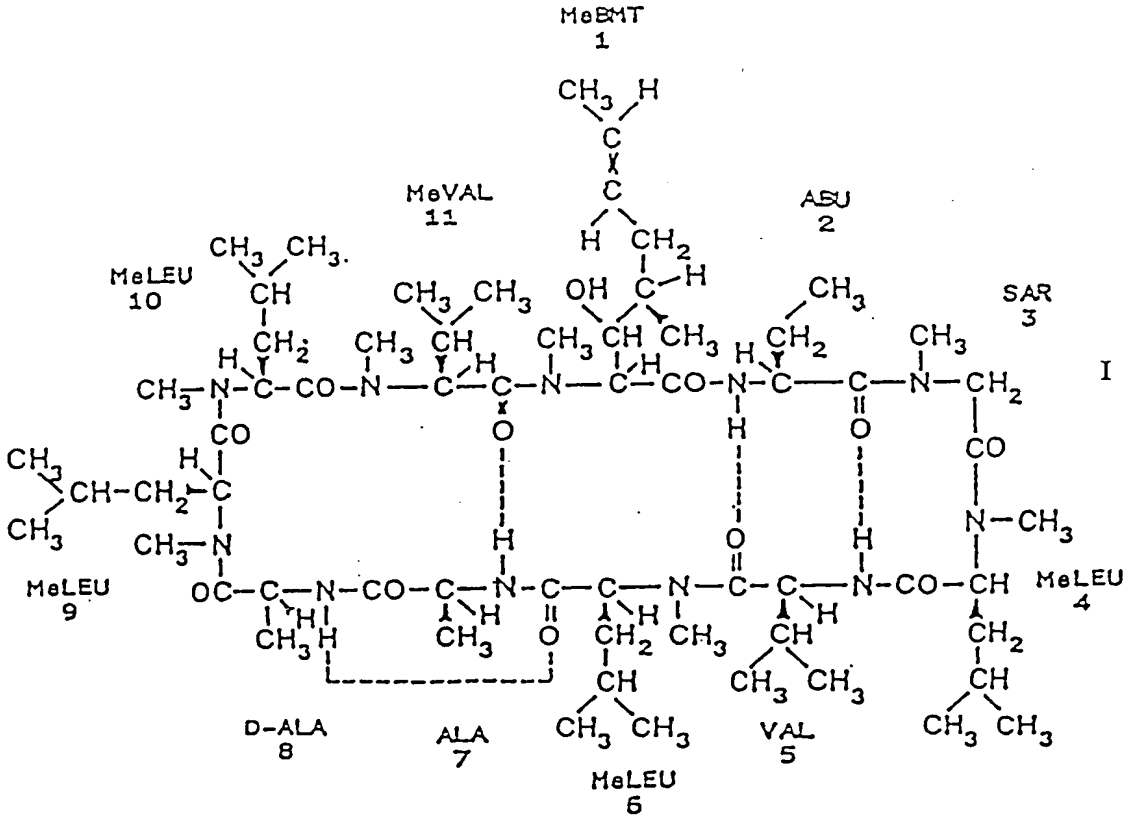
MEDICAL PREPARATIONS CONTAINING N-METHYLATED CYCLIC UNDECAPEPTIDES

TECHNICAL FIELD

The present invention concerns medical preparations for internal use, or for another use, containing poly-N-methylated monocyclic undecapeptides called cyclosporins.

BACKGROUND ART

This group of stucturally similar peptides called cyclosporins is produced by some deuteromycetes, such as e. g. Tolypocladium inflatum (Swiss pat. 589 716 and 603 790) or Tolypocladium terricola (Matha at al., Fytobios 69, 163 - 170, 1992). Besides cyclosporin A (=ciclosporin) of formula I a number of structurally similar natural cyclosporins was isolated (Traber et al., Helv. Chim. Acta 65, 1655 - 1667, 1982). Modified cyclosporins which were prepared by partial synthesis were described also in EPA 0216 122 or in Czechoslovak patent 277 472.



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Especially immunosuppressive properties of systemically administered ciclosporin are used in therapy or during organ transplants or bone marrow transplants. It is also applicable in treatment of broad range of autoimmune diseases of inflammatory etiology and also as antiparasitic treatment. Ciclosporin is used e. g. in rheumatic diseases (rheumatoid polyarthritis), hematologic diseases (aplastic anemia, idiopathic thrombocytopenia), gastric disorders (ulcerating colitis, Crohn disease), dermatic diseases (psoriasis, sclerodermia) and eye diseases (uveitis). Also topical applications have been tested e. g. in treatment of psoriasis, uveitis and allopecia.

Bioavailability of ciclosporin varies between 20 - 50 % for currently available dosage formulations (Wood A. J., et al., Transplant Proc., 15, suppl. 2409, 1983). There are significant differences between groups of patients. E. g. there is a low bioavailability in liver acceptors, and increased bioavailability in bone marrow transplantation. The interpersonal variability of biovailability is considerably greater, ranging from a few percent to 90 %. This is complicated also by the presence of significant variations in the course of the treatment.

Effective immunosuppressive treatment requires keeping a certain level of ciclosporin in blood and maintaining this level in certain range. The range required is always specific depending upon therapeutic goal. E. g. in cases of graft rejection or in treatment of autoimmune disease, it is necessary to take into account application of another immunosuppressant at the same time. When formulating medical drugs with cyclosporins, it is important to take into account their high lipophilicity. Solubility of these drugs in water

varies usually from 1.6 - 2.3 mg/100 ml and does not exceed 4mg/100 ml. Cyclosporins are not sufficiently resorbed from usual carriers in both liquid or solid state. This problem is solved in Swiss patent 636013 by using sezame oil and/or non-ionogenic tenside and/or reesterified non-ionogenic triglyceride and/or a mixture containing one or more lecithins, reeesterified non-ionogenic triglycerides or ethyloleate and/or neutral oil.

Another Swiss patent 641356 is trying ot improve resorption of cyclosporins by adding transesterification products of triglycerides with polyethylenglycols and/or saturated triglyceride of fatty acid and/or mono or diglycerides.

Therapeutically suitable concentrations of cyclosporins in liquid carriers show low stability towards precipitations from the solutions and the solutions are usually badly tolerated. Injection preparations containing a non-ionogenic tenside (Cremophor EL) can develop the anaphylactic reaction (Lorenc W. et al.: Agents and Actions 12, 64 - 80, 1982) and cause washing out of additives from plastic parts of devices for parenteral applications.

An oral formualtion with transesterification product of triglyceride with polyethylenglycols (Labrafil M 1914 C) forms an emulsion of v/o type in which phases are easily separated.

Insufficient tolerance of injection ciclosporin preparations containing non-ionogenic tensides was solved in a French patent 2608427 by preparing a lyophilisate for ad hoc formulation of sub-microne suspension. However, this process is energy-consuming when working with larger volumes of carrier containing ethanol.

Frequent undesirable side effects of ciclosporin treatment include nefrotoxicity, hypertension, hyperkalemia, hyperurikemia, hepatotoxicity, anemia, gastrointestinal intolerance, tremor and parestesia. The most frequent side effect is usually renal dysfunction. Acute ciclosporin nefrotoxicity is dose-dependent. There is a correlation with the blood level and a decrease in the dose or discontinuation of ciclosporin therapy leads to an improvement. However, progressive and irreversible damage of kidneys was reported in patients with transplants.

A composition of ciclosporin preparation with decreased nephrotoxicity containing omega 3 group of unsaturated fatty acids from fish oils was described in published interantional patent application WO 87/06463. A disadvantage of this form is considerable instability of the polyunsaturated fatty acids towards oxidative effects and unpleasant taste and odour.

The same is possible to say about similar ciclosporin formulations based on esential unsaturated fatty acids of evening primrose oil (Oenothera biennis and Oenothera Lamarckiana), borago oil (Borago officinalis) covered by published international patent application WO 90/03793 or black currant oil (Ribes nigrum) which is described in published european patent application EP 0 321 128.

BRIEF DESCRIPTION OF DRAWINGS

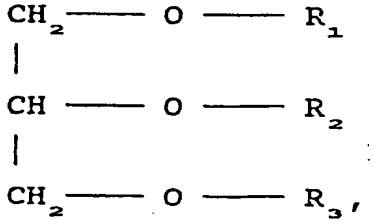
Fig. 1. depicts a scheme of multi-layered grid structure of aluminium-magnesium hydroxystearate of empirical formula $Al_5Mg_{10}/OH/C_{31}./C_{17}H_{35}COO/_4$. Figures 2 and 3 shows a graph comparing a dependence of ciclosporin concentration in blood on time after application of the preparation according to invention

and comercial product to Beagle dogs. The determination of the blood levels was made by means of RIA methods with specific antibodies (figure 2) and non-specific antibodies (figure 3).

DISCLOSURE OF INVENTION

The principle of new medical preparations with N-methylated cyclic undecapeptides, which are developed especially for internal use, is in the fact that they contain 0.1 to 20 weight parts of compounds /A/ from the group of cyclosporins, 0.3 to 60 weight parts of an emulsifier /B/ composed of anhydromannitol oleylether and/or lactoglyceride and/or citroglyceride, 0.1 to 10 weight parts of emulsion stabilizer /C/ composed of aluminium-magnesium hydroxystearate of empirical formula $Al_5Mg_{10}/OH/C_{31}./C_{17}H_{35}COO/_4$ in a form of lipogel and 0.2 to 40 weight parts of a solvent /D/ composed of 1,4 : 3,6-dianhydro-2,5-di-O-methyl-D-glucitole and/or 1,3-dimethyl-2-imidazolidinone and/or ethanol. The ratio A : B is from 1 : 0,5 to 1 : 30.

The compounds from the group of cyclosporins are either ciclosporin or /NVa/^{2} ciclosporin. The medical drugs prepared according to the present invention may contain also physiologically acceptable carrier based upon synthetic or plant oil with interfacial tension 10 $mN.m^{-1}$ to 25 $mN.m^{-1}$. Lactoglyceride or citroglyceride contain preferably at least 90 % of triglycerole of general formula



where at least one of the substituents R_1, R_2, R_3 is rest of lactic acid or citric acid, one is rest of fatty acid C_{14} to C_{18} and the last one is rest of lactic acid or citric acid, rest of fatty acid C_{14} to C_{18} or hydrogen atom. The medical preparations for external application contain preferably 1,3-dimethyl-2-imidazolidinone as a solvent.

The preparations according to the invention are proposed as self-emulgating dispersions of water/oil type stabilized by lipogel of aluminium-magnesium hydroxystearate. The emulsion part consists of a mixture of non-ionogenic tensides with the individual value HLB equal to 4 - 11, which do not contain ethyleneoxide units. With regard to characteristic emulgation properties of the tensides used, the external continuous lipophilic phase is selescted in such a way as to be formed of more polar oils with polarity index 10 - 25 $mN.m^{-1}$. Amphiphillic liquids of higher boiling point are used as solvents of cyclosporins. These liquids are miscible with water and most of organic solvents. They consist of 1,4:3,6-dianhydro-2,5-di-O-methyl-D-glucitole and 1,3-dimethyl-2-imidazolidinone or physiologically acceptable ethanol. The emulsifier anhydromanitol oleylether /Montanid 103 Seppic/ is a liquid of HLB 6.5 which is biodegradable by pancreatic lipases after oral application. It is characterized by the following physico-chemical parameters:

density /20°C/	0.97
viscosity /25°C/	cca 350 mPa.s
index of refraction /23°C/	1.474 - 1.475
iodine number	51 - 60
saponification number	120 - 136
hydroxyl number	95 - 110
acidity number	max. 1.5
peroxide number	max. 2.0 (mmol/kg)

Citroglycerides and lactoglycerides form the second group of emulsifiers used in the preparations made according to the invention. These are composed of mixed triacylglycerols where one or two hydroxyl groups are esterified by fatty acids and two or one glycerole hydroxyl is esterified by lactic acid or citric acid. These emulsifiers are made in several commercial brands, especially for food industry and they are marketed under the trade mark AXOL (Th. Goldschmidt AG). Lactoglyceride AXOL L61, L62 and citroglyceride AXOL C62 are typical representatives of these emulsifiers and they are characterized by the following physico chemical parameters:

	AXOL L61	AXOL L62	AXOLC62
melting point	48-53°C	≈ 45°C	58-64°C
saponification number	220-260	> 295	215-265
iodine number	max. 3	max. 3	max. 3
free fatty acids	max. 3 %	max. 3 %	max. 3 %
HLB	5 ± 1	6 ± 1	10 ± 1

Metabolic studies showed that these emulsifiers were totally hydrolyzed in the gastrointestinal tract giving rise to glycerol, fatty acids and corresponding hydroxycarboxylic acids. Experiments with labelled

formed when needed, e. g. before dilution, before application or during contact with body fluids. It is however desirable to achieve homogenous dispersion without special devices or elevated temperature. This can be achieved by special additives adjusting rheology. These additives can be in a form of lipogel aluminium magnesium hydroxystearate in plant oils. These lipogels are commercially available as GILUGEL (Giulini Chemie). For the preparations according to the present invention, the following types are most suitable: Gilugel MIG containing 80 % of neutral oil MIGLYOL 812, Gilugel ALM containing 80 % of almond oil and Gilugel CAO containing 80 % of castor oil. Gilugel MIG and Gilugel ALM are characterized by the following physico chemical data:

	Gilugel MIG	Gilugel ALM
content of Al	0.7 - 1.4 %	0.7 - 1.4 %
content of Mg	1.7 - 2.8 %	1.7 - 2,8 %
content of $Al_5Mg_{10}/OH/_{31}$ $/C_{17}H_{35}COO/_4$	20 %	20 %
content of water	0.4 - 1.2 %	0.1 - 0.4 %
density	0.985 - 0.995	0.97

The multilayer grid structure of Gilugel is characterised in scheme figure 1.

Modified - release of ciclosporin is achieved by arrangment of the ratio of emulsifiers and stabilizing agent. It is documented by fig. 2 and fig. 3 where time dependencies of blood levels are compared for commercially available product and for the preparation according to the present invention when applied to Beagle dogs.

In relation to emulsifiers used, triacylglycerols are suitable carriers, provided their polarity, expressed as the interfacial tension, is in the range 10 - 25 $mN.m^{-1}$. For example the following oil can be used: castor oil /13.7/, milk thistle oil /14.8/, olive oil /16.9/, almond oil /20.3/, and Miglyol 812 /21.3/.

Favourable for use in the preparations according the invention is the milk thistle oil, prepared from the seed of Silybum marianum by cold pressure or solvent extraction. The fatty acids part of the oil comprises:

palmitic acid	7.5 - 12.5 %
stearic acid	3.5 - 6.5 %
oleic acid	20.0 - 35.0 %
linoleic acid	46.0 - 65.0 %
linolenic acid	up to 5.0 %
gadolenic acid	up to 1.0 %
behenic acid	up to 2.5 %

The solvent 1,4 : 3,6-dianhydro-2,5-di-O-methyl-D--glucitol under the name Arlasolve DMI is produced by the company ICI American Inc. It has the following physico chemical properties:

boiling point	approx. 234°C
density 25°C	1,164
refractive index	1,467
viscosity 25°C	approx. 5 mPa.s
dielectric constant	approx. 7

The solvent 1,3-dimethyl-2-imidazolidinone is produced by Mitsui Toatsu Chemicals. Both compounds are characterized by high dissolving power for cyclosporins. 1,3-dimethyl-2-imidazolidinone is especially suitable for topical formulations due to its structural similarity with urea which improves skin hydration.

Preparations according to present invention were verified in two pharmacological models in 3 concentrations as described further on.

Influence of topical ciclosporin upon contact dermatitis induced in guinea pigs by 2,4-dinitrofluorobenzene (DNFB).

The topical preparation was tested in three concentrations (2 %, 1 % and 0.1 %) against placebo.

Albine twings (females, weight 300 - 500 g) were used. The animals were sensitized on the base of both ears by 50 µl of 2 % or 5 % DNFB (Aldrich Chemie, Germany) dissolved in a mixture of acetone - olive oil (1 : 1). The animals were shaved and depilated after 6 days (Opilca) on both sides. On the following day, 20 µl of 0.5 % DNFB dissolved in a mixture aceton : olive oil (4 : 1) was applied on both sides. Immediately afterwards, 250 mg of the ciclosporin was applied on the right side while 250 mg of the placebo was applied on the lift side. Two controls were used in the experiment - control 1 (negative with only 20 µl of

0.5 % DNFB being applied to both sides) and control 2 (positive, non treated with the compounds tested). The following parameters were assessed: skin thickness (measured one day before, 8, 24, 32, 48 hours after application) and erythrema (evaluated 24 and 32 hours after application). A size of the oedema was determined by subtracting the values measured one day before the application. The erythrema was assessed according to the following scale: 4 - protruding and dark red spot, 3 - red spot, 2 - pink spot, 1 - spread small points of pink colour, 0 - no change. The experiment was repeated twice - the animals were sensitized by 5 % or 2 % DNFB.

The effect of the compounds tested upon the oedema is depicted in the figure 1a and 1b. Ciclosporin influenced positively development of the oedema in comparison with the placebo with all concentrations used. The effect of the compounds upon the erythrema is summarized in the following table. Statistical evaluation was performed by Student t-test. Abbreviation CY A is used for ciclosporin (cyclosporin A).

Sensibilization with 5 % DNFB

	no. of animals	erythrema	
		24 hrs	32 hrs
Control 1	3	0 ± 0	0 ± 0
Control 2	5	2.40 ± 0.52	2.10 ± 0.88
CY A 0.1 %	5	0.40 ± 0.55 *	0.60 ± 0.55
CY A 1 %	5	0 ± 0 ***	0.20 ± 0.45 **
CY A 2 %	5	0.20 ± 0.45 **	0.20 ± 0.45 **
placebo	5	1.27 ± 1.03	1.13 ± 0.64

Sensibilization with 2 % DNFB

	no. of animals	erythrema 24 hrs	erythrema 32 hrs
Control 1	3	0.50 ± 0.55	0.50 ± 0.55
Control 2	5	2.20 ± 0.63	1.50 ± 0.71
CY A 0.1 %	5	0.20 ± 0.45 ***	0.40 ± 0.55 *
CY A 1 %	5	0 ± 0 ***	0.20 ± 0.45 **
CY A 2 %	5	0 ± 0 ***	0 ± 0 ***
placebo	5	1.67 ± 0.82	1.27 ± 1.03

Statistical evaluation was performed by Student t-test and was related to placebo.

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Effect of topical ciclosporin on DTH (a reaction of delayed hypersensitivity) induced by picrylchloride in mice.

The topical preparation was tested in three concentrations 2 %, 1 % and 0.1 % in comparison with ciclosporin placebo. A modified method was used as described by Descotes at al.: Meth. and Find. Exptl. Clin. Pharmacol., 7 (6) : 303 - 305, 1985. The inbred mice C57BL10/ScSn (females, weight 18 - 22 g) were used for the experiment. Abdomens of the animals were shaved on the day 0 and 200 µl of 5 % picrylchloride was applied to abdomen and paws. The picrylchloride was dissolved in 100 % ethanol. After 7 days, thickness of ears was measured and 50 µl of 1 % picrylchloride was applied on both ears. Immediately afterwards, 10 mg of topical ciclosporin was applied to right ear and 10 mg of corresponding placebo was applied to left ear.

Ear thickness was measured again after 14 hours. The value of oedema was obtained by subtracting ear thickness after and before the application of picrylchloride. Two controls were used for the experiment: control 1 (negative, only 50 µl of 1 % PiCl was applied on both ears) and control 2 (positive, not treated by the compounds tested). Statistical evaluation was performed by Student t-test and related to placebo. Each group contained 10 animals. The following table shows that both ciclosporin and placebo have beneficial effect upon the oedema induced by picrylchloride. A dose dependence was observed for the effect of ciclosporin. 2 % concentration was the most effective and showed statistically significantly better than placebo alone.

	Oedema (mm)	%
Control 1	0.031 ± 0.015	42.5
Control 2	0.073 ± 0.030	100.0
CY A 0.1 %	0.016 ± 0.016	21.9
CY A 1 %	0.015 ± 0.012	20.5
CY A 2 %	0.009 ± 0.009 ***	12.3
placebo	0.024 ± 0.020	32.9

Application of high-boiling solvents (Arlasolve DMI, b. p. 234°C or 1,3-dimethyl-2-imidazolidinone, b. p. 225°C) eliminates familiar problems with storage of existing oral concentrates and gelatine capsules based on ethanol which require a special packaging material. The capsules are usually packed in a single bed alu-foil packaging which makes the preparation rather voluminous and expansive while liquid concentrates require special leak-proof bottles with a rubber stop per secured by an aluminium capsule.

nine Beagle dogs. Male animals, aged 12 through 36 month, body weight of 9 to 13 kg. They were feed with standard pelleted diet in daily dose of 300 g witch free acces to drinking water. Doses were administered in the morning, after 18 hours starwation and swalloving was checked. Next feed was administered 12 hours later.

Samples of blood were taken in the following intervals: 0-0.5-1-2-4-6-8-10-12-24 hours after administration. Samples were frozen and stored at -20°C until the amalysis by means RIA method with the specific antibodies, the nonspecific antibodies or HPLC method was done.

In the course of the average concentrations of ciclosporin in blood in the dependence on time, determinated by specific RIA (Fig. 2) and non-specific RIA methods (Fig. 3) in the commercial product and the preparation according to this invention (example 5), there is the evidence to achieve the modified release of ciclosporin in the coarse of first 10 hours after the administration of the preparation according to this invention by decreasing of amount of emulsifier with simultaneous increasing of stabilizing agent in the preparation according to the invention there is possible to increase bioavailability of ciclosporin from separate formulations mentioned in the examples 6 and 2 by the increasing of the portion of emulgator.

Time	Example No. 6			
	HPLC		HPLC	
	Capsules		Capsules fill	
	$\bar{x}$ [µg/l]	S.E.	$\bar{x}$ [µg/l]	S.E.
0.5	168.00	40.62	340.20	142.27
1.0	721.40	152.36	819.90	87.28
2.0	1259.90	199.84	1177.30	85.446
4.0	951.60	189.51	753.10	78.79
6.0	628.20	123.70	557.20	97.90
8.0	541.00	115.62	431.10	74.22
10.0	521.40	100.27	368.80	70.75
12.0	394.80	68.09	338.70	79.49
24.0	114.50	32.13	169.70	43.52

Time	Example No.2			
	HPLC		Specific.RIA	
	Capsules fill		Capsules fill	
	$\bar{x}$ [µg/l]	S.E.	$\bar{x}$ [µg/l]	S.E.
0.5	526.30	158.15	417.83	178.60
1.0	1421.30	277.32	1416.50	253.92
2.0	1634.20	215.39	1713.33	192.49
4.0	1016.80	124.19	1259.67	154.09
6.0	761.20	126.27	999.06	209.70
8.0	648.10	137.54	799.00	122.51
10.0	593.60	126.39	627.33	88.74
12.0	466.80	93.98	562.33	70.49
24.0	190.20	49.64	197.83	52.26

It is possible to rich bioekvivalence between separate dosage forms as confirm pharmacokinetic data of commercial product and prepartion according to the invention, example No. 2.

	Commercial product	Example No.2
AUC_{0-ion}	11790.58	14336.42
C_{max}	1985.50	1999.50
t_{max}	2	2
K_a	3.431	3.725
$t^{(a)}_{1/2}$	0.202	0.198
K_e	0.215	0.173
$t^{(e)}_{1/2}$	3.276	4.043
MRT	6.243	7.389
V_d	80.380	81.968
CL	17.357	14.514

List of abbreviations used

AVC	area under the curve of concentration - time dependence [$\mu g.l^{-1}.h$]
C_{max}	maximum concentration obtained [$\mu g.l^{-1}$]
T_{max}	time to reach the concentration-time dependence curve peak [h]
K_a	first order absorption rate constant [h^{-1}]
$t_{1/2}^{(a)}$	absorption half-life time [h]
K_e	first order elimination rate constant [h^{-1}]
$t_{1/2}^{(b)}$	elimination half-life time [h]
MRT	mean residend time [h]
V_d	volume of distribution [l]
CL	total body clearence [$l.h^{-1}$]

MODES FOR CARRYING OUT THE INVENTION

The following examples show some compositions of preparations made according to the invention without having any limiting meaning.

1. Soft gelatine capsule

Composition:	Ciclosporin	1.500 kg
	Arlasolve DMI	2.250 kg
	Montanide 103	2.500 kg
	Axol C62	0.500 kg
	Gilugel MIG	1.000 kg
	Miglyol 812	up to 12.000 litres

Method of preparation:
Axol C62 and Miglyol 812 are mixed at 65°C and Gilugel MIG is disperged into a homogenous mixture. A solution of ciclosporin in Arlasolve DMI and Montanide 103 is added and stirred until the temperature drops to ambient. The preparation is filled into gelatine capsules on a suitable equipment (e. g. Pharmagel Mark III) in such a way that capsules No. 10 and 20 contain 75 and 150 mg of ciclosporin respcetively.

2. A concentrate for oral application

Composition:	Ciclosporin	1.000 kg
	Arlasolve DMI	1.500 kg
	Montanide 103	3.000 kg
	Axol L61	1.000 kg
	Gilugel MIG	1.000 kg
	Milk thistle oil	up to 10.000 litres

Method of preparation:
Axol L61 is mixed with milk thistle oil at 55°C and Gilugel MIG is disperged in the homogenous mixture. The dispersion is mixed with a solution of ciclosporin in Arlasolve DMI and Montanide 103 and the mixture is stirred until cooling down to ambient temperature. The preparation is filled into glass ampoules under protective atmosphere of inert gas. The ampoules are marked by volumetric signs.

3. Suppositorium

Composition:	/NVa/² ciclosporin	1.500 kg
	Arlasolve DMI	1.500 kg
	Montanide 103	1.000 kg
	Axol L61	1.500 kg
	Gilugel CAO	0.500 kg
	Witepsol H5	up to 9.000 litres

Method of preparation:
Axol L61 is mixed with Witepsol H5 at 55°C and Gilugel CAO is disperged into the homogenous mixture. A solution of /NVa/² ciclosporin in Arlasolve DMI and Montanide 103 are added and the solution is stirred until cooling down to ambient temperature. The prepartion is filled on a suitable device into gelatine suppositories of the following sizes:
No. 75 (= 675 mg/NVa/² ciclosporin)
No. 15 (= 150 mg/NVa/² ciclosporin)
No. 5 (= 50 mg/NVa/² ciclosporin)

4. Cream

Composition:	Ciclosporin	2.000 g
	1,3-dimethyl-2-imidazolidinon	10.000 g
	Axol C62	40.000 g
	Gilugel ALM	20.000 g
	Water	up to 100.000 g

Method of preparation:
Axol C62 is heated to 65°C and mixed with Gilugel ALM. The mixture is added to a solution of ciclosporin in 1,3-dimethyl-2-imidazolidinone and stirred in a

turbohomogenizer. Water heated to 70°C is added at the same time. After the prescribed volume is reached the mixture is stirred by a frame stirrer until cooling down to ambient temperature. The mixture is then filled into containers with mechanical dosage aplicator SP30.

5. Oral concentrate

Composition:	Ciclosporin	10.000 kg
	ethanol	8.000 kg
	Montanide 103	15.000 kg
	Gilugel MIG	15.000 kg
	Miglyol 812	up to 100.000 litres

Method of preparation:
Ciclosporin is dissolved in ethanol and mixed with Montanide 103. Miglyol 812 is mixed with Gilugel MIG. The ciclosporin solution is added to oil fraction and the mixture is homogenized. The preparation (100 mg/ml) is applied diluted by water or a suitable drink.

6. Oral concentrate

Composition:	Ciclosporin	10.000 kg
	Arlasolve DMI	15.000 kg
	Montanide 103	20.000 kg
	Axol C62	10.000 kg
	Gilugel MIG	10.000 kg
	Miglyol 812	up to 100.000 litres

Method of preparation:
Axol C62 is heated to 65°C and mixed with Miglyol 812. To the homogenous mixture is added the solution of ciclosporin in Arlasolve DMI and Montanide 103, than is

stirred until cooling down to ambient temperature. In the mixture is disperged Gilugel MIG by colloid mill. The preparation is filled to gelatine capsules or in the suitable containers.

INDUSTRIAL APPLICABILITY

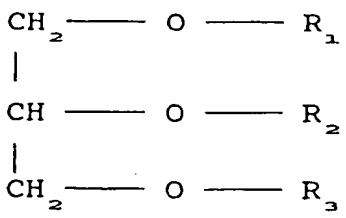
The invention is usable in pharmaceutical industry in manufacturing of immunosuppressive preparations and treating of autoimmune diseases.

0.1 to 20 weight parts of [illegible] of cyclosporines, 0.3 to 60 weight parts of emulsifiers /B/ containing anhydromanitol oleylether and/or lactoglyceride and/or citroglyceride, 0.1 to 10 weight part of emulsion stabilizer /C/ containing aluminium-magnesium hydrosystearate of empirical formula $Al_5Mg_{10}/OH/_{31}./C_{17}H_{35}COO/_4$ in a form of lipogel and 0.2 to 40 weight parts of solvent /D/ containing 1,4:3,6-dianhydro-2,5-di-O-methyl-D-glucitole and/or 1,3-dimethyl-2-imidazolidinone and/or ethanol with the ratio A:B equal 1:0.5 to 1:30.

2. Medical preparations according to claim 1, characterized by the presence of physiologically acceptable carrier based on synthetic or plant oil with interfacial tension in the range 10 $mN.m^{-1}$-25 $mN.m^{-1}$.

3. Medical preparations according to claim 1, characterized by the fact that the compounds from the group of cyclosporins are either ciclosporin or /NVa/^{2} ciclosporin.

4. Medical preparations according to claim 1, characterized by the fact thet the lactoglyceride or citroglyceride contain at least 90 % of triacylglycerole of general formula



where at least one of the substituents R_1, R_2, and R_3 is rest of lactic acid or rest of citric acid, another is a rest of fatty acid C_{14} to C_{18} and the last one rest of lactic acid or rest of citric acid or rest of fatty acid C_{14} to C_{18} or hydrogen atom.

5. Medical preparations according to claim 1 for external application, characterized by content of 1,3-dimethyl-2-imidazolidinone used as a solvent.

$Al_5 Mg_{10} (OH)_{31} (C_{17} H_{35} COO)_4$

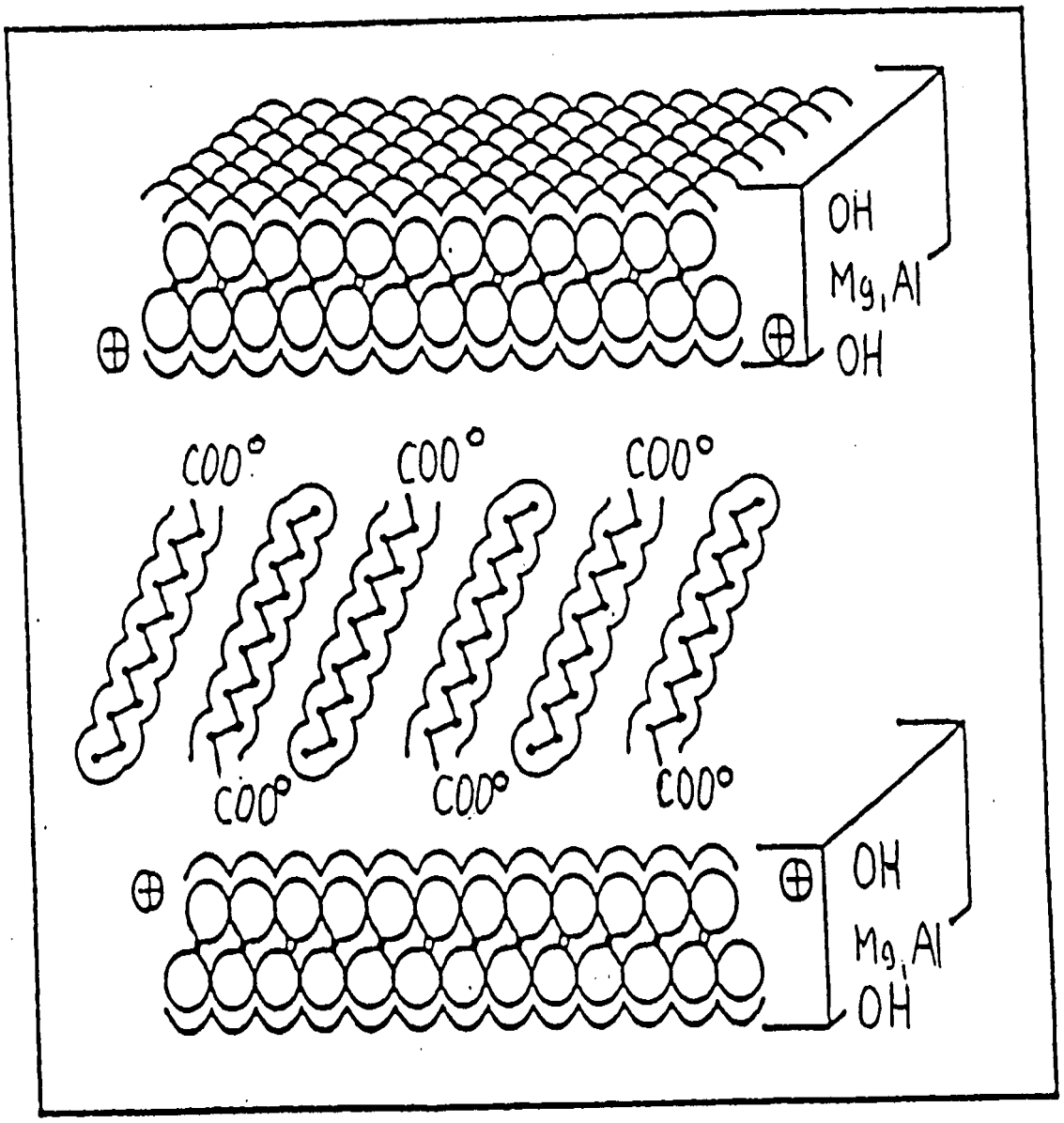


Fig. 1

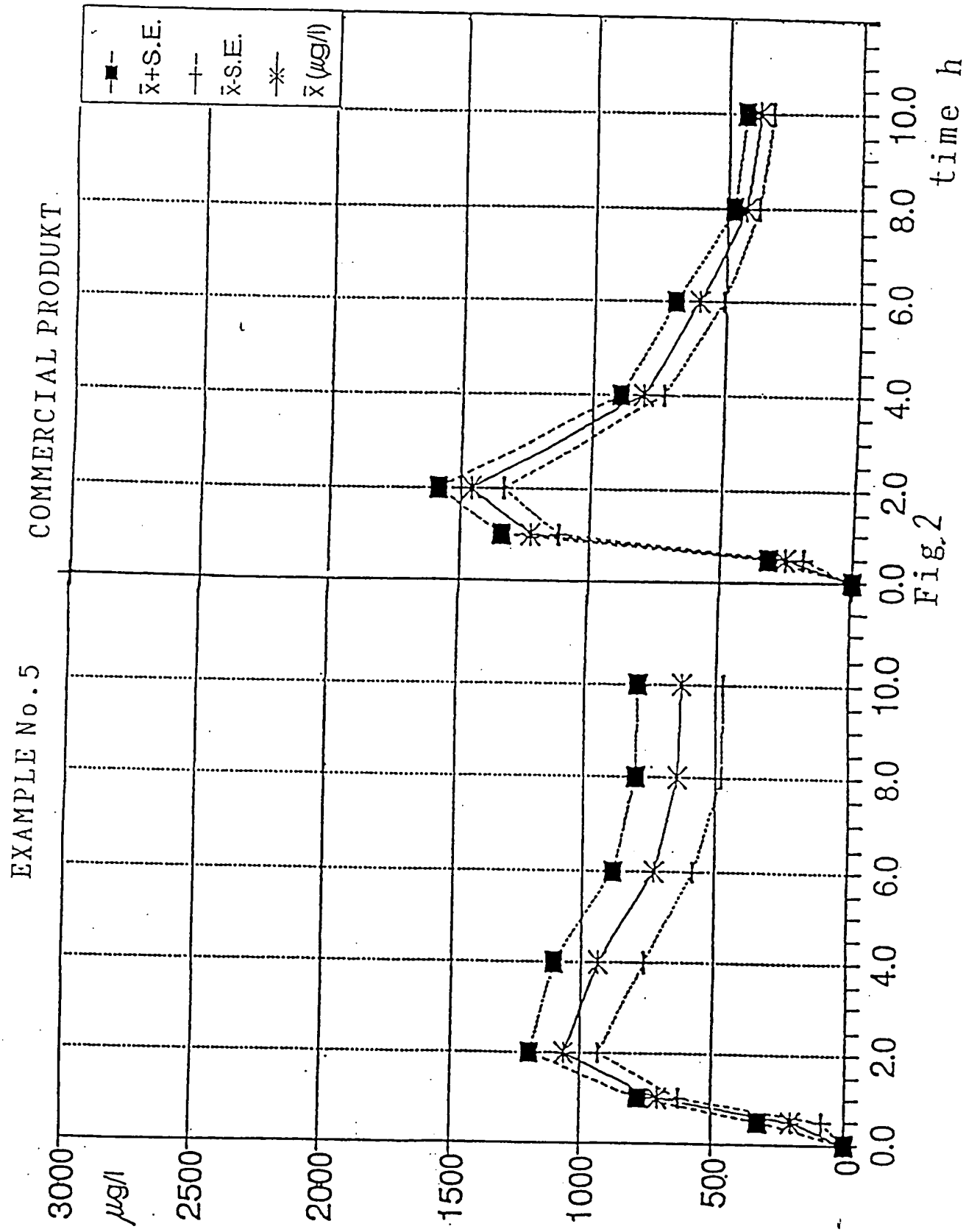

EXAMPLE No.5
COMMERCIAL PRODUKT
x̄+S.E.
x̄-S.E.
x̄ (µg/l)
µg/l
3000
2500
2000
1500
1000
500
0
0.0
2.0
4.0
6.0
8.0
10.0
time h

Fig.2

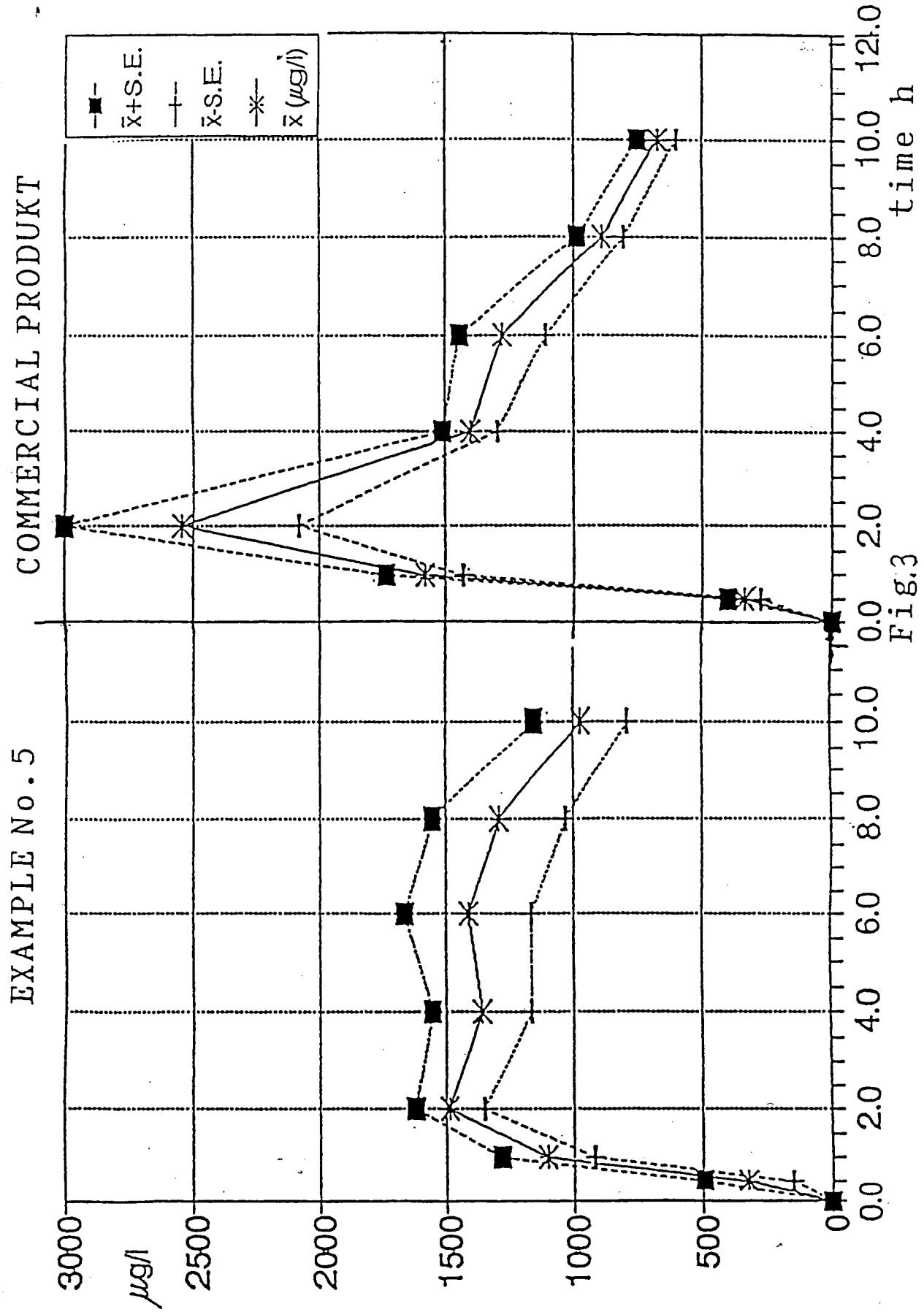

COMMERCIAL PRODUKT
EXAMPLE No.5
x̄+S.E.
x̄-S.E.
x̄ (µg/l)
µg/l
3000
2500
2000
1500
1000
500
0
0.0
2.0
4.0
6.0
8.0
10.0
12.0
time h

Fig.3

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/CZ 93/00022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K37/02 A61K47/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 242 205 (NORDEN LABORATORIES INC.) 21 October 1987 see claims 1,4 see example 2 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 1993	28.12.93.

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/CZ 93/00022

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0242205	21-10-87	US-A-	4806350	21-02-89
		AU-B-	609667	02-05-91
		AU-A-	7176087	22-10-87
		CA-A-	1282003	26-03-91
		JP-A-	62255436	07-11-87